Health Care Resource Utilization, Costs, and Persistence in Patients Newly Diagnosed as Having Nonvalvular Atrial Fibrillation and Newly Treated With Dabigatran versus Warfarin in the United States

Tim Bancroft, PhD[1]; Jonathan Lim, MSc, MEng[2]; Cheng Wang, MD, PhD[2]; Stephen D. Sander, PharmD[2]; and Jason P. Swindle, PhD, MPH[1]

[1]Health Economics and Outcomes Research, Inc., Optum, Eden Prairie, Minnesota; and [2]Health Economics and Outcomes Research, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut

ABSTRACT

Purpose: This study compared health care resource utilization (HCRU), costs, and persistence among patients newly diagnosed as having nonvalvular atrial fibrillation (NVAF) and newly treated with dabigatran versus warfarin.

Methods: This retrospective claims-based study used data from a large US managed care organization. The earliest claim for dabigatran or warfarin during October 1, 2010 through October 31, 2011 was the index date, with cohort assignment based on index medication. Evidence of newly diagnosed NVAF within 30 days before the index date and no claims for oral anticoagulants during the 12-month preindex period were required. Cohorts were matched using propensity scores. Per-patient-per-month HCRU, costs, and persistence were calculated during the variable follow-up period of up to 12 months after the index date. Descriptive and multivariable analyses were used to examine differences in outcomes.

Findings: After matching, 869 patients per cohort were identified (mean age, 67.8 years; 40.4% female). Compared with warfarin, dabigatran had fewer per-patient-per-month emergency department (0.10 vs 0.13, $P = 0.010$), office (1.98 vs 2.96, $P < 0.001$), and outpatient (1.05 vs 1.48, $P < 0.001$) visits. Despite higher mean pharmacy costs for dabigatran ($P < 0.001$), mean total health care ($P = 0.309$) and medical costs ($P = 0.568$) were similar to warfarin. Persistence was higher with dabigatran versus warfarin (median, 204 vs 161 days; mean, 213.7 vs 195.5 days, $P = 0.001$).

Implications: Among patients newly diagnosed as having NVAF, those newly treated with dabigatran had lower HCRU, higher persistence, and similar total health care costs compared with those treated with warfarin. (*Clin Ther*. 2016;38:545–556) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: dabigatran, health care costs, health care resource use, persistence, warfarin.

INTRODUCTION

Atrial fibrillation (AF) is the most common clinical arrhythmia and a major cause of stroke. In the United States alone, an estimated 1 in 4 adults 40 years and older will develop AF during their lifetime,[1] placing them at 4- to 5-fold higher risk of stroke.[2] Strokes attributable to AF are associated with greater mortality, morbidity, and risk of recurrence than non-AF strokes.[3] The annual incremental cost of AF in the United States is estimated at $8705 per patient (2008 US dollars), reflecting greater use of both inpatient and outpatient services.[4] Extrapolated to the 2010 US population, the national incremental burden attributable to AF is in the range of $6 billion to $21 billion annually (2008 US dollars).[4]

Warfarin, a vitamin K antagonist, is an oral anticoagulant (OAC) effective in reducing stroke risk in patients with AF.[5] However, warfarin has a narrow therapeutic range, requiring regular blood monitoring and dose adjustments to maintain the target international normalized ratio (INR) within 2.0 to 3.0.[6] US patients with AF maintain an INR within the

Accepted for publication January 25, 2016.
http://dx.doi.org/10.1016/j.clinthera.2016.01.008
0149-2918/$ - see front matter

© 2016 The Authors. Published by Elsevier HS Journals, Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

therapeutic range a mean of 55% of the time.[7] Underanticoagulation, as evidenced by an INR <2.0, increases the risk and severity of ischemic stroke,[8,9] whereas overanticoagulation (INR >3.0) increases bleeding risk.[9] There are considerable drug and food interactions with warfarin,[10] which can also compromise INR control. Both INR testing and the consequences of poor INR control consume considerable health care resources.[11–13]

Dabigatran,[14] a direct thrombin inhibitor, is an OAC approved by the Food and Drug Administration in the United States in October 2010 to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF), which represents approximately 95% of AF cases.[15] Dabigatran offers several advantages over warfarin. First, INR testing is not required to maintain therapeutic levels. Next, in the pivotal Randomized Evaluation of Long-Term Anticoagulant Therapy clinical trial, dabigatran was associated with lower rates of stroke and systemic embolism compared with adjusted-dose warfarin.[16] Furthermore, in real-world clinical practice, patients newly diagnosed as having NVAF who initiate OAC therapy with dabigatran were more likely to persist with therapy than their counterparts initiating warfarin therapy.[17] However, the effect of these clinical advantages of dabigatran over warfarin on health care resource utilization (HCRU) in clinical practice has not been well characterized. The objective of this study was to compare real-world HCRU and costs among patients newly diagnosed as having NVAF who were newly treated with dabigatran versus warfarin. We also evaluated persistence to each OAC therapy during the first year of treatment.

METHODS

Study Design and Data Source

This retrospective claims-based study used medical, pharmacy, and enrollment data from a large US managed care organization affiliated with Optum, Inc. The patient index date was identified based on the date of initiation of dabigatran or warfarin treatment. Because dabigatran was approved in October 2010, the patient identification period began on October 1, 2010 continuing through October 31, 2011. Data extracted for each patient covered 12 months before the index date and up to 12 months after the index date; therefore, the full study period spanned October 1, 2009 through October 31, 2012 (Figure 1). During the patient identification period, the database contained 15,316,248 commercial and Medicare Advantage Prescription Drug coverage enrollees with medical and pharmacy benefits. Medical claims data used for this study included *International Classification of Disease, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis and procedure codes, Healthcare Common Procedure Coding System codes, revenue codes, and paid amounts (combined health plan plus patient paid amounts). Pharmacy claims data used for this study included National Drug Codes for filled prescriptions, days supplied, quantity of drug supplied, and paid amounts. All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act.

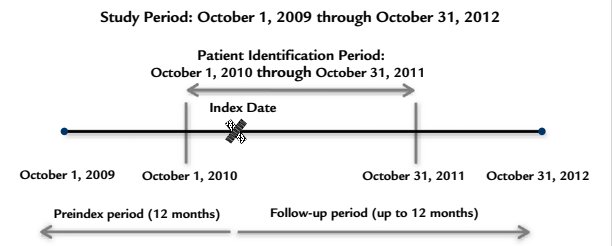

Figure 1. Study design.

Patient Identification and Study Cohorts

The study sample comprised patients newly diagnosed as having NVAF and newly treated with dabigatran or warfarin. The index date was defined as the first pharmacy claim for dabigatran or warfarin (index OAC) during the patient identification period.

Patients were identified for inclusion in the study in a sequential manner. First, all patients were required to have ≥1 inpatient claim (ie, medical claim associated with inpatient stay) or ≥2 office visit or emergency department (ED) claims (ie, medical claims associated with office or ED visits or a combination thereof) with a diagnosis code for AF (*ICD-9-CM* code 427.31 in any position) in the 12 months before the index date.[4,17–19] Patients were also required to have continuous health plan enrollment with medical and pharmacy benefits for 12 months before the index date (defined as the preindex period) and up to 12

months after (and including) the index date (defined as the follow-up period). End of follow-up was defined as the earliest of health plan disenrollment, medication discontinuation (or switch) from the index OAC, death, 12 months after the index date, or end of study period (October 31, 2012). The earliest medical claim with diagnosis code for AF during the preindex period was defined as the first AF claim.

To distinguish NVAF from AF, patients with ≥1 medical claim with evidence of valvular heart disease (Supplemental Table I) were excluded. In the interest of excluding transient and secondary NVAF, patients with ≥1 medical claim with evidence of cardiac surgery, myocarditis, pericarditis, or pulmonary embolism (Supplemental Table I) within 30 days before the first AF claim were excluded. In addition, patients <18 years old on the index date and patients with ≥1 medical claim with evidence of hyperthyroidism (Supplemental Table I) during the preindex period were excluded. The remaining patients were then required to have ≥2 pharmacy claims on separate dates for the index OAC (dabigatran or warfarin) during the follow-up period, including the pharmacy claim for the OAC on the index date.

Finally, the criteria of newly diagnosed NVAF and newly treated with dabigatran or warfarin were applied: newly diagnosed NVAF was defined as the occurrence of first AF claim within 30 days before the index date; patients with claim(s) for AF that occurred before 30 days from the index date (ie, days 31–365 before the index date) were excluded. Newly treated was defined as no pharmacy claims for any OAC (dabigatran, rivaroxaban, or warfarin) during the preindex period. Patients were then assigned to either the dabigatran or warfarin cohort according to the index OAC.

Patient Characteristics

Age, sex, geographic location, and health plan type (commercial or Medicare Advantage Prescription Drug coverage) were reported as of the index date. The following clinical indexes were calculated during the preindex period: Deyo-Charlson comorbidity score,[20] $CHADS_2$[21] and CHA_2DS_2-VASc[22] stroke risk scores, and $HEMORR_2HAGES$ bleeding risk score.[23] The Deyo-Charlson comorbidity score is a predictor of mortality risk defined by 17 medical conditions. The $CHADS_2$ score is a predictor of stroke risk that incorporates patient age (>74 years) and history of chronic heart failure, hypertension, diabetes mellitus, and stroke/transient ischemic attack as risk factors; the CHA_2DS_2-VASc score includes 3 additional risk factors (female sex, age 65–74 years, and vascular disease). The $HEMORR_2HAGES$ score is a predictor of bleeding risk according to patient age (>75 years), medical history (hepatic or renal disease, alcohol abuse, malignant tumor, reduced platelet count or dysfunction, rebleeding risk, uncontrolled hypertension, anemia, stroke), genetic factors, and excessive fall risk. The presence or absence of clinically relevant conditions or events during the preindex period was identified based on *ICD-9-CM* diagnosis and procedure codes from preindex medical claims (Supplemental Table I). Preindex medication use was determined by pharmacy and medical claims and categorized as the presence or absence of any medication and as counts of individual medications or medication classes (Supplemental Table II). Health care costs (ie, medical and pharmacy) were calculated for the preindex period. All-cause total health care costs represented the sum of medical and pharmacy costs; all costs were inflation adjusted to 2012 US dollars.[24]

Outcomes

Persistence to index OAC represented the time to discontinuation or switch of index OAC. Discontinuation was defined as failure to refill (ie, an absence of a pharmacy claim for the index exposure within 30 days [permissible gap] of the run-out date of the previous claim for the index exposure). Patients who did not discontinue or switch index OAC were right-censored at the earliest of: health plan disenrollment, death, end of 12-month follow-up, or end of study period (October 31, 2012). Although warfarin treatment discontinuation has been previously defined by gaps in both prescription fill dates and INR testing,[25,26] a 30-day medication gap is a sensitive measure of discontinuation.[17]

Both HCRU and costs were calculated for the follow-up period and censored on the date of discontinuation or switch of index OAC (if either occurred). Because of variable length follow-up, HCRU and costs were reported as per-patient-per-month (PPPM). All-cause HCRU was defined as the counts of health care encounters, categorized as inpatient stay, ED visit, outpatient visit, and office

visit. All-cause health care costs were calculated as total costs (sum of medical and pharmacy costs), medical costs, and pharmacy costs; all costs were inflation adjusted to 2012 US dollars.[24]

Propensity Score Matching

Patients in the dabigatran and warfarin cohorts were 1:1 nearest neighbor matched using propensity score matching (PSM) with a caliper of 0.2 of the SD of the estimated logit. Propensity scores were calculated by logistic regression modeling with the following predictor variables: age, sex, health plan type, geographic location, and index month and preindex characteristics, namely, Deyo-Charlson comorbidity score, $CHADS_2$ score, $HEMORR_2HAGES$ score, presence or absence of comorbidities (Supplemental Table I), all-cause medical costs, all-cause pharmacy costs, index prescriber specialty, time from first AF claim to index date, and presence or absence of medication use (Supplemental Table II).

Statistical Analysis

Between-cohort comparisons of pre-PSM, preindex characteristics were conducted with 2-sample *t* tests with Satterthwaite adjustment where appropriate (continuous variables) and χ^2 tests (categorical variables). Between-cohort comparisons of post-PSM, preindex characteristics and outcomes during follow-up were conducted with paired *t* tests (continuous variables) and Rao-Scott tests (categorical variables).

Multivariable regression models adjusting for preindex characteristics were constructed to examine cohort differences in follow-up all-cause health care costs and time to index therapy discontinuation or switch. Time to index therapy discontinuation was modeled with Cox proportional hazards. The estimated time to therapy discontinuation was also described graphically using the Kaplan-Meier estimator of the cumulative hazard rate. All-cause total health care, medical, and pharmacy costs were modeled with Lin's regression,[27,28] which accounts for censored follow-up time and cost accumulation at multiple intervals. With this method, the follow-up period is partitioned into twelve 30-day intervals during which costs are accumulated and the cost within each 30-day interval is weighted by the probability of survival during each interval. The SEs for 12-month adjusted costs are based on 1000 bootstrapped samples.

All regression models included index OAC and the following adjustment variables: age, sex, geographic location, health plan type, presence or absence of preindex stroke, Deyo-Charlson comorbidity score, CHA_2DS_2-VASc score, $HEMORR_2HAGES$ score, and log-transformed preindex all-cause total health care costs. In addition, other covariates serving as adjustment variables only were included based on stepwise selection using $P = 0.05$ for both entry and retention in the model. Adjustment variables subject to stepwise selection were index prescriber specialty (cardiology or other) and the following preindex characteristics: presence or absence of selected comorbid conditions (cancer, rheumatoid arthritis, multiple sclerosis, coronary artery disease, acute myocardial infarction, cardiomyopathy, transient ischemic attack, ischemic stroke, heart failure, atrial flutter, hypertension, peripheral artery disease, liver disease, renal disease, chronic obstructive pulmonary disease or emphysema, hypothyroidism, diabetes, peptic ulcer or gastroesophageal reflux disease, venous thromboembolism, hyperlipidemia, Human Immunodeficiency Virus (HIV) infection, bone marrow disease, coagulopathy, dyspepsia, bleeding), the count of concomitant medication classes, pharmacy claims, all-cause outpatient visits, all-cause office visits, all-cause ED visits, and total length (days) of all inpatient stays.

RESULTS

Patient Identification and Characteristics

A total of 49,448 patients with NVAF and ≥ 2 claims for either dabigatran (7013 patients) or warfarin (42,435 patients) on or after the index date were identified (**Figure 2**). Among these patients, 1010 were newly diagnosed as having NVAF and newly treated with dabigatran, and 3200 were newly diagnosed as having NVAF and newly treated with warfarin. After PSM, 869 patients in each cohort were retained.

The pre- and post-PSM characteristics of each cohort for key matching variables are given in **Table I**; the full complement of matching variables and other characteristics of interest are given in Supplemental Table III. Among all matched patients, the mean age was 67.8 years, 40.4% were female, and most patients (64.7%) had commercial insurance. The mean time from first AF claim to index date was just >1 week and similar between cohorts (8.7 and 8.4 days for dabigatran and warfarin, respectively; P=0.343). The mean Deyo-Charlson, $CHADS_2$, CHA_2DS_2-VASc, and $HEMORR_2HAGES$ scores were also similar between cohorts. After matching, clinical characteristics were

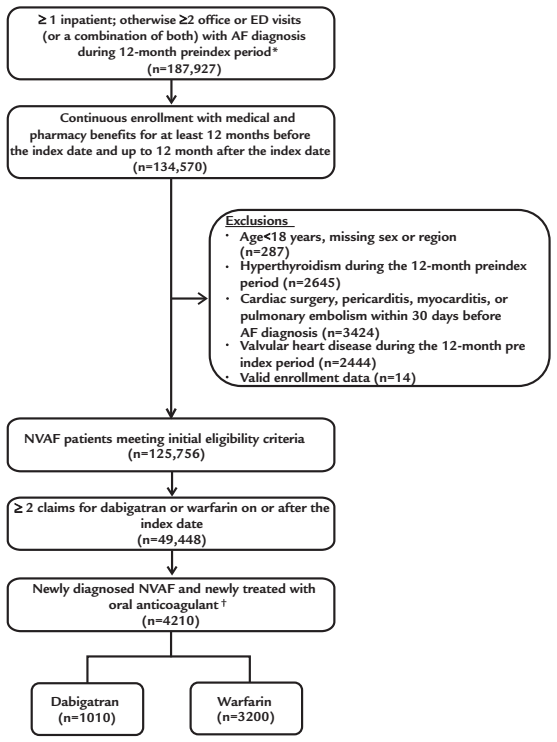

Figure 2. Patient sample identification. AF = indicates atrial fibrillation; ED = emergency department; NVAF = nonvalvular atrial fibrillation. *Index date is first pharmacy claim for warfarin or dabigatran (index oral anticoagulant) during the patient identification period (October 1, 2010 through October 31, 2011). †Newly diagnosed NVAF was defined as the occurrence of the first AF claim within 30 days before the index date, and newly treated was defined as no claims for oral anticoagulant (dabigatran, rivaroxaban, or warfarin) during the 12-month preindex period.

similar between cohorts for all matched variables with the exception of preindex bleeding. Compared with the warfarin cohort, a slightly higher proportion of dabigatran-treated patients had preindex bleeding (6.2% vs. 4.0%, $P = 0.037$).

HCRU and Costs

All-cause HCRU (PPPM) of the dabigatran and warfarin cohorts during follow-up is given in Table II. The dabigatran cohort had significantly fewer ED visits (0.10 vs 0.13, $P = 0.010$), office visits (1.98 vs 2.96, $P < 0.001$), and outpatient visits (1.05 vs 1.48, $P < 0.001$) than the warfarin cohort. The mean counts of inpatient stays were lower for the dabigatran cohort, but the difference was not statistically significant between cohorts ($P = 0.093$).

Adjusted 12-month, mean all-cause health care costs are presented in Table III. Similar to the unadjusted cost results, although pharmacy costs were higher for the dabigatran cohort ($P < 0.001$), total health care ($P = 0.318$) and medical ($P = 0.750$) costs were similar for both cohorts.

Persistence

Measures of persistence with index OAC are given in Table IV and Figure 3. Compared with the warfarin cohort, a lesser proportion of patients in the dabigatran cohort discontinued therapy (51.9% vs 61.6%, $P < 0.001$), and dabigatran-treated patients continued to receive therapy longer (median days, 204.0 vs 161.0; mean days, 213.7 vs 195.5; $P = 0.001$). The Kaplan-Meier probabilities of persistence were greater for the dabigatran cohort throughout the 365-day follow-up period ($P < 0.001$). In the adjusted Cox proportional hazards analysis, the dabigatran cohort had 21.5% lower risk of treatment discontinuation (hazard ratio, 0.785; 95% CI, 0.692-0.890; $P < 0.001$).

DISCUSSION

Our results provide important insights into the real-world HCRU and costs of patients newly diagnosed as having NVAF who are newly treated with dabigatran versus warfarin. Patients newly treated with dabigatran had less all-cause HCRU than patients taking warfarin. Patients initiating OAC therapy with dabigatran were also more likely to be persistent with therapy in the first year of treatment than those patients taking warfarin.

Patients newly treated with dabigatran had lower mean all-cause HCRU in the ambulatory setting than warfarin-treated patients. The dabigatran cohort incurred a mean of 33% fewer office and 29% fewer outpatient visits. Higher ambulatory service utilization among warfarin-treated patients likely reflects in part the incremental burden of regular INR testing and dose adjustments for patients managed with warfarin. A recent study of 5 US claims databases indicated that

Table I. Patient demographic and clinical characteristics before and after PSM.

Characteristic*	Before PSM			After PSM		
	Dabigatran (n = 1010)	Warfarin (n = 3200)	*P* value†	Dabigatran (n = 869)	Warfarin (n = 869)	*P* value‡
Age, mean (SD), y	66.9 (11.3)	72.0 (11.2)	<0.001	67.7 (11.5)	67.9 (11.6)	0.698
Female, no. (%)	397 (39.3)	1477 (46.2)	<0.001	345 (39.7)	357 (41.1)	0.547
Geographic location, no. (%)						
Northeast	115 (11.4)	341 (10.7)	0.515	100 (11.5)	87 (10.0)	0.323
Midwest	261 (25.8)	1265 (39.5)	<0.001	248 (28.5)	245 (28.2)	0.870
South	528 (52.3)	1260 (39.4)	<0.001	425 (48.9)	427 (49.1)	0.924
West	106 (10.5)	334 (10.4)	0.958	96 (11.1)	110 (12.7)	0.305
Health plan type, no. (%)						
Commercial	692 (68.5)	1231 (38.5)	<0.001	559 (64.3)	566 (65.1)	0.691
MAPD coverage	318 (31.5)	1969 (61.5)	<0.001	310 (35.7)	303 (34.9)	0.691
Time from first AF claim to index date, d						
Mean (SD)	8.9 (8.1)	8.4 (7.3)	0.084	8.7 (8.0)	8.4 (7.5)	0.343
Median	6.0	6.0		5.0	5.0	
Preindex clinical index scores, mean (SD)						
Deyo-Charlson comorbidity index	1.73 (1.80)	2.49 (2.09)	<0.001	1.85 (1.84)	1.86 (1.81)	0.967
$CHADS_2$	1.91 (1.24)	2.44 (1.30)	<0.001	2.00 (1.24)	2.01 (1.21)	0.903
CHA_2DS_2-VASc	3.09 (1.76)	3.95 (1.78)	<0.001	3.23 (1.77)	3.26 (1.73)	0.749
$HEMORR_2HAGES$	2.28 (1.65)	3.14 (1.99)	<0.001	2.41 (1.69)	2.33 (1.58)	0.320
Preindex conditions or events, no. (%)						
Hyperlipidemia	699 (69.2)	2248 (70.3)	0.529	605 (69.6)	590 (67.9)	0.444
Diabetes mellitus	304 (30.1)	1184 (37.0)	<0.001	271 (31.2)	258 (29.7)	0.495
Heart failure	244 (24.2)	1256 (39.3)	<0.001	237 (27.8)	243 (28.0)	0.737
Peptic ulcer or GERD	181 (17.9)	752 (23.5)	<0.001	159 (18.3)	169 (19.5)	0.532
COPD or emphysema	180 (17.8)	644 (20.1)	0.108	153 (17.6)	171 (19.7)	0.272
Cardiomyopathy	134 (13.3)	498 (15.6)	0.075	121 (13.9)	125 (14.4)	0.784
Hypertension	127 (12.6)	605 (18.9)	<0.001	114 (13.1)	105 (12.1)	0.520
Ischemic stroke	95 (9.4)	403 (12.6)	0.006	85 (9.8)	92 (10.6)	0.574
Transient ischemic attack	78 (7.7)	281 (8.8)	0.294	66 (7.6)	74 (8.5)	0.483

(continued)

Table I. (continued).

Characteristic*	Before PSM			After PSM		
	Dabigatran (n = 1010)	Warfarin (n = 3200)	*P* value†	Dabigatran (n = 869)	Warfarin (n = 869)	*P* value‡
Bleeding	55 (5.5)	340 (10.6)	<0.001	54 (6.2)	35 (4.0)	0.037
Venous thromboembolism	14 (1.4)	353 (11.0)	<0.001	14 (1.6)	9 (1.0)	0.252
Preindex (12-month) all-cause total health care costs, mean (SD), $§	16,679 (20,001)	23,826 (32,132)	<0.001	17,342 (20,839)	17,578 (21,023)	0.810
Duration of follow-up, d						
Mean (SD)	208.2 (129.7)	200.1 (128.9)	0.084	210.6 (130.4)	193.6 (125.4)	0.003
Median	186.5	171.0		194.0	159.0	

AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; MAPD = Medicare Advantage Prescription Drug; PSM = propensity score match; SD = standard deviation.

*The following preindex variables were used for PSM: age, sex, plan type, geographic location, index month, Deyo-Charlson comorbidity score, $CHADS_2$ score, $HEMORR_2HAGES$ score, comorbidities (heart failure, diabetes mellitus, cardiomyopathy, COPD or emphysema, hyperlipidemia, peptic ulcer or GERD, stroke or transient ischemic attack, hypertension, venous thromboembolism, bleeding), index prescriber specialty, time from first AF claim to index exposure, and concomitant medication use (argatroban, unfractionated heparin, enoxaparin, tinzaparin, dalteparin, fondaparinux, β-blockers, calcium channel blockers, diuretics, other antihypertensives [angiotensin-converting enzyme inhibitors, angiotensin receptor blockers], antihyperlipidemics, corticosteroids, antidiabetics, antiarrhythmics [amiodarone, propafenone, flecainide, dronedarone, sotalol, dofetilide, disopyramide, quinidine], ketoconazole, antiplatelets, nonsteroidal anti-inflammatory drugs).

†Two-sample *t* test with Satterthwaite adjustment where appropriate (continuous variables) and χ^2 test (categorical variables).

‡Paired *t* test (continuous variables) and Rao-Scott test (categorical variables).

§All-cause preindex health care costs was not a PSM variable.

Table II. All-cause HCRU during follow-up.

Visit Type	PPPM Count of HCRU, Mean (SD)* Dabigatran (n = 869)	Warfarin (n = 869)	P†
Inpatient stays	0.06 (0.15)	0.07 (0.18)	0.093
ED visits	0.10 (0.27)	0.13 (0.31)	0.010
Office visits	1.98 (1.67)	2.96 (2.16)	<0.001
Outpatient visits	1.05 (1.42)	1.48 (1.81)	<0.001

ED = emergency department; HCRU = health care resource utilization; PPPM = per-patient-per-month.
*Propensity score matched cohorts.
†Paired *t* test.

patients with AF who undergo INR testing have a mean of 0.5 to 2.0 INR tests per month.[29] We also observed 26% lower mean utilization of all-cause ED services for dabigatran-treated patients. Greater utilization of ED services may reflect suboptimal INR control among some warfarin-treated patients. The percentage of time spent outside the INR therapeutic range among warfarin-treated patients is considerable,[7,9] and patients with poor anticoagulation control have worse clinical outcomes, including a higher risk of stroke and bleeding events, which drive higher and more costly resource utilization.[12,19,30] However, our results are based on all-cause utilization, and we cannot ascribe the overall higher HCRU in the warfarin cohort to specific events, such as INR testing, stroke, or bleeding. As expected, all-cause pharmacy costs were higher for the dabigatran cohort, given that dabigatran is available as a branded medication. However, all-cause total health care and medical costs were similar for both treatment cohorts, suggesting that dabigatran is a cost-neutral alternative to warfarin.

According to the Cox proportional hazards analysis, patients taking dabigatran were 21.5% less likely to discontinue or switch therapy than warfarin-treated patients. The Kaplan-Meier probabilities of patients remaining on therapy at 1 year were 43.4% for the dabigatran cohort and 33.0% for the warfarin cohort. Given that dabigatran is a relatively new option in anticoagulation, there are limited comparator studies based on large claims databases in the peer-reviewed literature.[17,31] Our results can be most readily compared with the findings of Zalesak et al,[17] whose study

Table III. All-cause health care costs during follow-up.

Cost Type	Mean Adjusted 12-Month All-Cause Health Care Costs, $ Dabigatran* (n = 869)	Warfarin* (n = 869)	P†
Total (medical plus pharmacy)	25,369.89	23,430.14	0.318
Medical	19,194.98	19,814.64	0.750
Pharmacy	6121.92	3459.48	<0.001

*Propensity score matched cohorts.
†The 12-month total health care costs were evaluated using Lin's regression, adjusted for age, sex, geographic location, health plan type, and the following preindex characteristics: ischemic stroke, heart failure, liver disease, bone marrow disease, Deyo-Charlson comorbidity score, CHA_2DS_2-VASc score, $HEMORR_2HAGES$ score, all-cause emergency department visits, and all-cause inpatient days.

Table IV. Persistence with dabigatran and warfarin during follow-up.

Variable	Dabigatran* (n = 869)	Warfarin* (n = 869)	*P*
Discontinued, no. (%)	451 (51.9)	535 (61.6)	<0.001‡
Switch, no. (%)	25 (6.0)	38 (4.4)	0.127‡
Persistence, d			
Mean (SD)	213.7 (129.6)	195.5 (125.6)	0.001†
Median	204.0	161.0	
Kaplan-Meier persistence probability, %			<0.001§
90 Days	77.7	74.6	
180 Days	61.5	53.9	
270 Days	50.7	40.2	
365 Days	43.4	33.0	

*Propensity score matched cohorts.
†Paired *t* test.
‡Rao-Scott test.
§Log-rank test.

methods most closely resembled what we used to create newly diagnosed and newly treated NVAF cohorts and to define persistence. In the study by Zalesak et al,[17] 1-year persistence was 50.3% for dabigatran versus 24.1% warfarin. Dabigatran persistence was somewhat higher than we observed, which may be partially a function of differences in patient preindex characteristics between the 2 studies. For

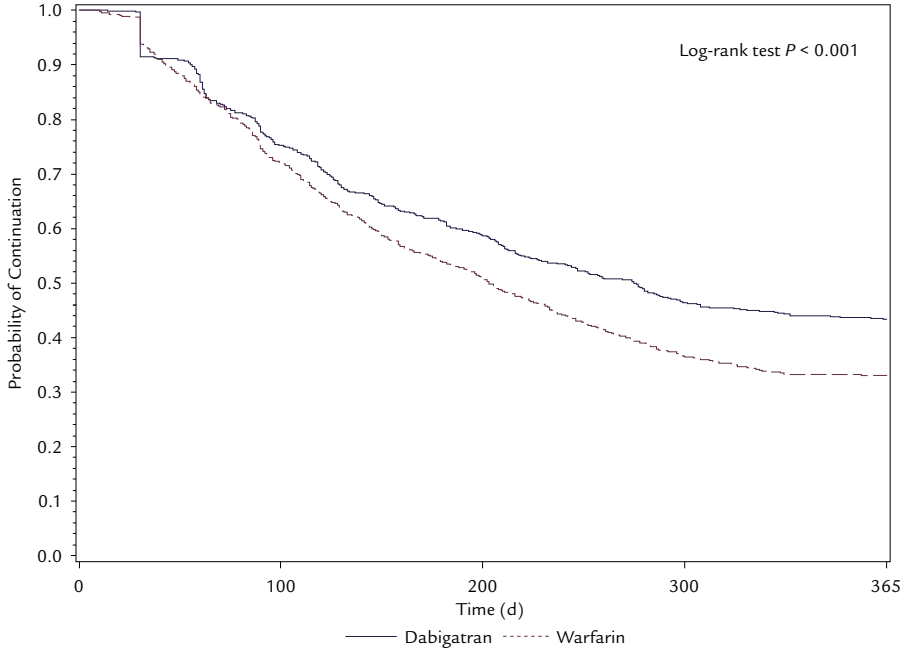

Figure 3. Kaplan-Meier probability of persistence.

example, younger age and lower stroke risk ($CHADS_2$ score <2) were predictors of nonpersistence to dabigatran in the previous study (which analyzed predictors of nonpersistence separately for each OAC cohort). The dabigatran cohort in our study was younger (68 vs 73 years) and had lower mean $CHADS_2$ scores (2.0 vs 2.3) than the previous study. However, Zalesak et al[17] also observed that higher Deyo-Charlson comorbidity score and higher bleeding risk ($HEMORR_2HAGES$ score >3) were predictive of nonpersistence to dabigatran, and dabigatran-treated patients in our study had lower mean Deyo-Charlson comorbidity scores (1.85 vs 2.5) and slightly lower $HEMORR_2HAGES$ scores (2.4 vs 2.6). Younger age, lower $CHADS_2$ scores, and bleeding events are also known risk factors for nonpersistence with warfarin therapy.[32–35] Additional research is needed to determine the degree to which these patient characteristics and possibly other factors predict persistence to dabigatran in clinical practice.

The prevalence of AF is projected to increase 2.5- to 3-fold between 2000 and 2050.[15,36,37] Underutilization of warfarin[38] and low persistence rates with warfarin therapy[35] place patients with AF at considerably greater risk of stroke and the sequelae of higher HCRU and costs. Our results suggest that dabigatran offers benefits in terms of lower HCRU and higher medication persistence, with total health care costs that are similar to warfarin.

Study Limitations

Certain limitations that are inherent to claims-based analyses should be considered when interpreting the results of this study. The entire medical history of a patient is not available in claims databases, and the information that was captured in this study was limited to the study period. The presence of a diagnostic code on a medical claim is not proof positive of the presence of disease. To strengthen the selection of patients with evidence of AF, we required either an inpatient claim or ≥ 2 office or ED claims with diagnosis code for AF. We used PSM to maximize the balance in relevant patient characteristics between the dabigatran and warfarin cohorts; however, there may have been other unmeasured or unidentified factors that were not balanced among cohorts and could have influenced the outcomes. Unlike dabigatran, warfarin use may be subject to frequent dose adjustments based on INR test results, which may shorten or lengthen the duration of medication supply available in a single prescription fill. Our estimates of persistence are based on the earliest gap in index OAC supply >30 days. It is possible that persistence was overestimated or underestimated using this technique; however, previous research has found that 89% of warfarin and 95% of dabigatran medication gaps were <30 days[17]; thus, we would expect the degree of overestimation and underestimation to be similar between cohorts. Furthermore, pharmacy claims do not indicate whether the medication was taken or taken as prescribed. Finally, our results are based on patients with commercial or Medicare fee-for-service insurance and may not be generalizable to other populations.

CONCLUSIONS

Among patients newly diagnosed as having NVAF and newly treated with dabigatran or warfarin, those treated with dabigatran had significantly fewer office, outpatient, and ED visits than those taking warfarin. The all-cause total health care costs were similar among dabigatran- and warfarin-treated patients. Dabigatran-treated patients were also more likely to remain persistent and to do so for longer periods than warfarin-treated patients during the first year of treatment.

ACKNOWLEDGMENTS

Sarah Peirce-Sandner (Optum, Inc., Eden Prairie, MN) provided medical writing support for this manuscript, which was funded by Boehringer Ingelheim Pharmaceuticals, Inc.

T. Bancroft, J. Lim, S. D. Sander and C. Wang were involved in study concept and design. T. Bancroft conducted the data analysis. J. Lim participated in drafting the manuscript. All authors participated in interpretation of results, critical revision of the manuscript at each stage and approved the final manuscript.

CONFLICTS OF INTEREST

T. Bancroft and J. P. Swindle are employees of Optum, Inc. and were funded by Boehringer Ingelheim Pharmaceuticals, Inc, to conduct the study. J. Lim, C. Wang, and S. D. Sander are employees of Boehringer Ingelheim Pharmaceuticals, Inc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTARY INFORMATION

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.01.008.

REFERENCES

1. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110:1042–1046.
2. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946–952.
3. Miller PS, Andersson FL, Kalra L. Are cost benefits of anticoagulation for stroke prevention in atrial fibrillation underestimated? *Stroke*. 2005;36:360–366.
4. Kim MH, Johnston SS, Chu BC, et al. Estimation of total incremental health care costs in patients with atrial fibrillation in the United States. *Circ Cardiovasc Qual Outcomes*. 2011;4:313–320.
5. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–867.
6. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:1935–1944.
7. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm*. 2009;15:244–252.
8. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349:1019–1026.
9. Mearns ES, White CM, Kohn CG, et al. Quality of vitamin K antagonist control and outcomes in atrial fibrillation patients: a meta-analysis and meta-regression. *Thromb J*. 2014;12:14.
10. Holbrook AM, Pereira JA, Labiris R, et al. Systematic overview of warfarin and its drug and food interactions. *Arch Intern Med*. 2005;165:1095–1106.
11. Biskupiak J, Ghate SR, Jiao T, Brixner D. Cost implications of formulary decisions on oral anticoagulants in nonvalvular atrial fibrillation. *J Manag Care Pharm*. 2013;19:789–798.
12. Ghate SR, Biskupiak J, Ye X, et al. All-cause and bleeding-related health care costs in warfarin-treated patients with atrial fibrillation. *J Manag Care Pharm*. 2011;17:672–684.
13. Hallinen T, Soini EJ, Asseburg C, et al. Warfarin treatment among Finnish patients with atrial fibrillation: retrospective registry study based on primary healthcare data. *BMJ Open*. 2014;4:e004071.
14. Boehringer Ingelheim Pharmaceuticals Inc. PRADAXA® (dabigatran etexilate mesylate) capsules for oral use. 2014.
15. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370–2375.
16. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Committee R-LS, Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
17. Zalesak M, Siu K, Francis K, et al. Higher persistence in newly diagnosed nonvalvular atrial fibrillation patients treated with dabigatran versus warfarin. *Circ Cardiovasc Qual Outcomes*. 2013;6:567–574.
18. Francis K, Yu C, Alvrtsyan H, et al. Healthcare utilization and costs associated with dabigatran compared to warfarin treatment in newly diagnosed patients with non-valvular atrial fibrillation. *Curr Med Res Opin*. 2015:1–7.
19. Mercaldi CJ, Siu K, Sander SD, et al. Long-term costs of ischemic stroke and major bleeding events among medicare patients with nonvalvular atrial fibrillation. *Cardiol Res Pract*. 2012;2012:645469.
20. D'Hoore W, Bouckaert A, Tilquin C. Practical considerations on the use of the Charlson comorbidity index with administrative data bases. *J Clin Epidemiol*. 1996;49:1429–1433.
21. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.
22. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272.
23. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151:713–719.
24. US Department of Labor BoLS. Consumer Price Index. Chained Consumer Price Index.
25. Fang MC, Go AS, Chang Y, et al. Warfarin discontinuation after starting warfarin for atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2010;3:624–631.
26. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA*. 2003;290:2685–2692.
27. Lin DY. Linear regression analysis of censored medical costs. *Biostatistics*. 2000;1:35–47.

28. Lin DY. Regression analysis of incomplete medical cost data. *Stat Med*. 2003;22:1181–1200.
29. Lang K, Bozkaya D, Patel AA, et al. Anticoagulant use for the prevention of stroke in patients with atrial fibrillation: findings from a multipayer analysis. *BMC Health Serv Res*. 2014;14:329.
30. Cotte FE, Benhaddi H, Duprat-Lomon I, et al. Vitamin k antagonist treatment in patients with atrial fibrillation and time in therapeutic range in four European countries. *Clin Ther*. 2014;36:1160–1168.
31. Tsai K, Erickson SC, Yang J, et al. Adherence, persistence, and switching patterns of dabigatran etexilate. *Am J Manag Care.*. 2013;19:e325–e332.
32. Gallagher AM, Rietbrock S, Plumb J, van Staa TP. Initiation and persistence of warfarin or aspirin in patients with chronic atrial fibrillation in general practice: do the appropriate patients receive stroke prophylaxis? *J Thromb Haemost*. 2008;6:1500–1506.
33. Gomes T, Mamdani MM, Holbrook AM, et al. Persistence with therapy among patients treated with warfarin for atrial fibrillation. *Arch Intern Med*. 2012;172:1687–1689.
34. Hylek EM, Evans-Molina C, Shea C, et al. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation*. 2007;115:2689–2696.
35. Suh DC, Choi JC, Schein J, et al. Factors associated with warfarin discontinuation, including bleeding patterns, in atrial fibrillation patients. *Curr Med Res Opin*. 2013;29:761–771.
36. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125.
37. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol*. 2009;104:1534–1539.
38. Zimetbaum PJ, Thosani A, Yu HT, et al. Are atrial fibrillation patients receiving warfarin in accordance with stroke risk? *Am J Med*. 2010;123:446–453.

Address correspondence to: Jason P. Swindle, PhD, MPH, Health Economics and Outcomes Research, Optum, Inc. 11000 Optum Circle, Eden Prairie, MN 55344. E-mail: jason.swindle@optum.com

SUPPLEMENTARY MATERIALS

Tables I–III.

Table I. Supplemental codes

Conditions	Codes
Conditions used in sample selection	
Valvular heart disease	ICD-9-CM diagnosis codes (any position): 394.0x, 394.2, 396.0, 396.0 HCPCS codes: 33999, 0257T, 0258T, 0259T, 33405, 33425, 33426, 33427, 33430, 0262T, 33475, 33460, 33463, 33464, 33465
Cardiac surgery	ICD-9-CM procedure codes: 00.5x, 35.xx, 36.xx, 37.xx
Myocarditis	ICD-9-CM diagnosis codes (any position): 391.2, 422.xx, 074.23, 398.0, 429.0, 032.82, 036.43, 093.82, 130.3
Pericarditis	ICD-9-CM diagnosis codes (any position): 391.x, 393, 420.x, 423.2, 0.36.41, 074.21, 093.81, 098.83
Pulmonary embolism	ICD-9-CM diagnosis codes (any position): 415.1x
Hyperthyroidism	ICD-9-CM diagnosis codes (any position): 242.x
Pre-index conditions/events	
Cancer	ICD-9-CM diagnosis codes (any position): 140.xx-172.xx, 174.xx-208.xx, 230.xx-231.xx, 233.xx-234.xx
Rheumatoid arthritis	ICD-9-CM diagnosis codes (any position): 714.xx
Multiple sclerosis	ICD-9-CM diagnosis codes (any position): 340
Coronary artery disease	ICD-9-CM diagnosis codes (any position): 411.xx, 412.xx, 413.xx, 414.xx, 429.2
Acute MI	ICD-9-CM diagnosis codes (any position): 410.xx
Cardiomyopathy[a]	ICD-9-CM diagnosis codes (any position): 425.xx
Ischemic stroke[a]	ICD-9-CM diagnosis codes (any position): 433.x1, 434.x1, 436.x
TIA[a]	ICD-9-CM diagnosis codes (any position): 435.x
Heart failure[a]	ICD-9-CM diagnosis codes (any position): 402.x1, 404.x1, 404.x3, 428.xx
Atrial flutter	ICD-9-CM diagnosis codes (any position): 427.32
Hypertension[a]	ICD-9-CM diagnosis codes (any position): 401.x, 402.x0, 403.xx, 404.x0, 404.x2, 405.xx
Peripheral artery disease	ICD-9-CM diagnosis codes (any position): 440.xx, 443.xx
Liver disease	ICD-9-CM diagnosis codes (any position): 121.1, 423.2, 570-573.xx, 751.62
Renal disease	ICD-9-CM diagnosis codes (any position): 580.xx-588.xx, 590.xx-593.xx
COPD/emphysema[a]	ICD-9-CM diagnosis codes (any position): 490-492.xx, 496
Hypothyroidism	ICD-9-CM diagnosis codes (any position): 243-244.x
Diabetes[a]	ICD-9-CM diagnosis codes (any position): 250.xx
Peptic ulcer/GERD[a]	ICD-9-CM diagnosis codes (any position): 530.11, 530.81, 536.2, 536.8, 787.1, 533.xx
Venous thromboembolism[a]	ICD-9-CM diagnosis codes (any position): 415.11, 415.19, 451.1x, 451.2, 451.81, 451.83, 451.84, 451.9,453.4x, 453.8x, 453.9
Hyperlipidemia[a]	ICD-9-CM diagnosis codes (any position): 272.0–272.4
HIV infection	ICD-9-CM diagnosis codes (any position): V08, 042, 079.53

(continued)

Table I. (continued).

Conditions	Codes
Bone Marrow disease	ICD-9-CM diagnosis codes (any position): 287.3x, 287.4x, 287.5x, 285.2x, 289.83
Thrombocytopenia	ICD-9-CM diagnosis codes (any position): 287.3, 287.4, 287.5
Chronic anemia	ICD-9-CM diagnosis codes (any position): 285.2
Myelofibrosis	ICD-9-CM diagnosis codes (any position): 289.83
Coagulopathy (hemophilia/ Von Willebrand disease)	ICD-9-CM diagnosis codes (any position): 286.0-286.9, 287.1, 287.3-287.5
Dyspepsia	ICD-9-CM diagnosis codes (any position): 536.8
Bleeding[a]	ICD-9-CM diagnosis codes (primary position only): 455.2, 455.5, 455.8, 456.0, 456.20, 459.0, 530.7, 530.82, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578, 599.7, 719.1x, 786.3, 423.0, 593.81, 784.7, 784.8 ICD-9-CM diagnosis codes (any position): 430, 431, 432, 852.0x, 852.2x, 852.4x, 853.0

GERD, gastroesophageal reflux disease; HIV, Human Immunodeficiency Virus; MI, myocardial infarction; TIA, transient ischemic attack
[a]PSM match variables.

Table II. Pre-index medications

Medications	Medication Classes
Dabigatran	Beta blockers[a]
Rivaroxaban	Calcium channel blockers[a]
Warfarin	Diuretics[a]
Argatroban[a]	Other antihypertensives (angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers)[a]
Unfractionated heparin[a]	Antihyperlipidemics[a]
Enoxaparin[a]	Corticosteroids[a]
Tinzaparin[a]	Antidiabetics[a]
Dalteparin[a]	Antiarrhythmics (amiodarone, propafenone, flecainide, dronedarone, sotalol, dofetilide, disopyramide, quinidine)[a]
Fondaparinux[a]	Antiplatelets[a]
Ketoconazole[a]	Non-steroidal anti-inflammatory drugs[a]

[a]PSM match variables

Table III. Patient demographic and clinical characteristics before and after PSM for all matching variables and other comorbid conditions and risk scores

Characteristic*	Before PSM			After PSM		
	Dabigatran (n=1,010)	Warfarin (n=3,200)	*P* value†	Dabigatran (n=869)	Warfarin (n=869)	*P* value†
Age, mean (SD)	66.9 (11.3)	72.0 (11.2)	<0.001	67.7 (11.5)	67.9 (11.6)	0.698
Age group, n (%)						
18-34	4 (0.4)	8 (0.3)	0.448	4 (0.5)	3 (0.4)	0.706
35-44	21 (2.1)	48 (1.5)	0.206	16 (1.8)	19 (2.2)	0.612
45-54	116 (11.5)	187 (5.8)	<0.001	96 (11.1)	88 (10.1)	0.530
55-64	306 (30.3)	535 (16.7)	<0.001	238 (27.4)	232 (26.7)	0.749
65-74	287 (28.4)	934 (29.2)	0.638	249 (28.7)	249 (28.7)	1.000
75-79	114 (11.3)	555 (17.3)	<0.001	109 (12.5)	112 (12.9)	0.826
≥80	162 (16.0)	933 (29.2)	<0.001	157 (18.1)	166 (19.1)	0.562
Female, n (%)	397 (39.3)	1,477 (46.2)	<0.001	345 (39.7)	357 (41.1)	0.547
Geographic location, n (%)						
Northeast	115 (11.4)	341 (10.7)	0.515	100 (11.5)	87 (10.0)	0.323
Midwest	261 (25.8)	1,265 (39.5)	<0.001	248 (28.5)	245 (28.2)	0.870
South	528 (52.3)	1,260 (39.4)	<0.001	425 (48.9)	427 (49.1)	0.924
West	106 (10.5)	334 (10.4)	0.958	96 (11.1)	110 (12.7)	0.305
Health plan type, n (%)						
Commercial	692 (68.5)	1,231 (38.5)	<0.001	559 (64.3)	566 (65.1)	0.691
MAPD	318 (31.5)	1,969 (61.5)	<0.001	310 (35.7)	303 (34.9)	0.691
Time from first AF claim to index date, days, mean (SD)	8.9 (8.1)	8.4 (7.3)	0.084	8.7 (8.0)	8.4 (7.5)	0.343
Pre-index clinical indices						
Deyo-Charlson comorbidity index score, mean (SD)	1.73 (1.80)	2.49 (2.09)	<0.001	1.85 (1.84)	1.86 (1.81)	0.967
$CHADS_2$ score, mean (SD)	1.91 (1.24)	2.44 (1.30)	<0.001	2.00 (1.24)	2.01 (1.21)	0.903
$CHADS_2$ score group, n (%)						
0	93 (9.2)	154 (4.8)	<0.001	67 (7.7)	74 (8.5)	0.538
1	327 (32.4)	610 (19.1)	<0.001	258 (29.7)	241 (27.7)	0.342
2-6	590 (58.4)	2,436 (76.1)	<0.001	544 (62.6)	554 (63.8)	0.600
CHA_2DS_2-VASc score, mean (SD)	3.09 (1.76)	3.95 (1.78)	<0.001	3.23 (1.77)	3.26 (1.73)	0.749
$HEMORR_2HAGES$ score, mean (SD)	2.28 (1.65)	3.14 (1.99)	<0.001	2.41 (1.69)	2.33 (1.58)	0.320
$HEMORR_2HAGES$ score group, n (%)						
0-1	385 (38.2)	672 (21.0)	<0.001	302 (34.8)	290 (33.4)	0.534
2-3	424 (42.0)	1,398 (43.7)	0.340	375 (43.2)	417 (48.0)	0.042
4-12	201 (19.9)	1,130 (35.3)	<0.001	192 (22.1)	162 (18.6)	0.066
Elixhauser comorbidity index score, mean (SD)	3.22 (2.07)	4.54 (2.43)	<0.001	3.39 (2.09)	3.63 (2.19)	0.013

(continued)

Table III. (continued).

Characteristic*	Before PSM			After PSM		
	Dabigatran (n=1,010)	Warfarin (n=3,200)	*P* value†	Dabigatran (n=869)	Warfarin (n=869)	*P* value†
Pre-index conditions/events, n (%)						
Acute MI	66 (6.5)	272 (8.5)	0.045	64 (7.4)	64 (7.4)	1.000
Atrial flutter	841 (83.3)	2,773 (86.7)	0.007	730 (84.0)	725 (83.4)	0.751
Bone marrow disease (thrombocytopenia, chronic anemia, myelofibrosis)	40 (4.0)	251 (7.8)	<0.001	39 (4.5)	38 (4.4)	0.909
Bleeding	55 (5.5)	340 (10.6)	<0.001	54 (6.2)	35 (4.0)	0.037
Cancer	119 (11.8)	445 (13.9)	0.084			
Cardiomyopathy	134 (13.3)	498 (15.6)	0.075	121 (13.9)	125 (14.4)	0.784
COPD/emphysema	180 (17.8)	644 (20.1)	0.108	153 (17.6)	171 (19.7)	0.272
Coagulopathy (hemophilia, Von Willebrand disease)	26 (2.6)	206 (6.4)	<0.001	24 (2.8)	28 (3.2)	0.579
Coronary artery disease	374 (37.0)	1,363 (42.6)	0.002	338 (38.9)	331 (38.1)	0.727
Dyspepsia	13 (1.3)	47 (1.5)	0.671	12 (1.4)	13 (1.5)	0.842
Heart failure	244 (24.2)	1,256 (39.3)	<0.001	237 (27.8)	243 (28.0)	0.737
Diabetes mellitus	304 (30.1)	1,184 (37.0)	<0.001	271 (31.2)	258 (29.7)	0.495
HIV infection	2 (0.2)	4 (0.13)	0.592	1 (0.1)	1 (0.1)	1.000
Hyperlipidemia	699 (69.2)	2,248 (70.3)	0.529	605 (69.6)	590 (67.9)	0.444
Hypertension	127 (12.6)	605 (18.9)	<0.001	114 (13.1)	105 (12.1)	0.520
Ischemic stroke	95 (9.4)	403 (12.6)	0.006	85 (9.8)	92 (10.6)	0.574
Liver disease	181 (17.9)	1,044 (32.6)	<0.001	173 (19.9)	211 (24.3)	0.024
Left ventricular heart failure	172 (17.0)	555 (17.3)	0.818	156 (18.0)	132 (15.2)	0.125
Multiple sclerosis	0	10 (0.3)	0.075	0	6 (0.7)	-
Peptic ulcer/GERD	181 (17.9)	752 (23.5)	<0.001	159 (18.3)	169 (19.5)	0.532
Peripheral artery disease	42 (4.2)	177 (5.5)	0.087	38 (4.4)	35 (4.0)	0.718
Renal disease	196 (19.4)	908 (28.4)	<0.001	177 (20.4)	188 (21.6)	0.515
Rheumatoid arthritis	30 (3.0)	106 (3.3)	0.592	27 (3.1)	18 (2.1)	0.170
Transient ischemic attack	78 (7.7)	281 (8.8)	0.294	66 (7.6)	74 (8.5)	0.483
Venous thromboembolism	14 (1.4)	353 (11.0)	<0.001	14 (1.6)	9 (1.0)	0.252
Pre-index medication use, Anticoagulants, n (%)						
Argatroban	0	1 (0.03)	0.574	0	0	–
Unfractionated Heparin (Heparin)	35 (3.5)	162 (5.1)	0.036	32 (3.7)	30 (3.5)	0.793
Low Molecular Weight Heparins:						
Enoxaparin	38 (3.8)	200 (6.3)	0.003	37 (4.3)	37 (4.3)	1.000
Tinzaparin	0	0	–	0	0	–

(continued)

Table III. (continued).

Characteristic*	Before PSM			After PSM		
	Dabigatran (n=1,010)	Warfarin (n=3,200)	*P* value†	Dabigatran (n=869)	Warfarin (n=869)	*P* value†
Dalteparin	2 (0.2)	15 (0.5)	0.237	2 (0.2)	1 (0.1)	0.564
Fondaparinux	1 (0.1)	8 (0.3)	0.365	1 (0.1)	1 (0.1)	1.000
Other medications, n (%)						
Beta blockers (single agent; i.e., no fixed-dose combinations)	513 (50.8)	1,551 (48.5)	0.198	433 (49.8)	448 (51.6)	0.492
Calcium channel blockers (single agent; i.e., no fixed-dose combinations)	317 (31.4)	1,026 (32.1)	0.688	271 (31.2)	265 (30.5)	0.761
Diuretics (single agent; i.e., no fixed-dose combinations)	274 (27.1)	1,167 (36.5)	<0.001	254 (29.2)	257 (29.6)	0.873
Other antihypertensives (e.g., ACE inhibitors, ARBs, fixed-dose single pill combinations)	579 (57.3)	1,938 (60.6)	0.067	509 (58.6)	501 (57.7)	0.697
Antihyperlipidemics	537 (53.2)	1,645 (51.4)	0.329	465 (53.5)	439 (50.2)	0.207
Corticosteroids	211 (20.9)	740 (23.1)	0.139	189 (21.8)	199 (22.9)	0.568
Antidiabetics	198 (19.6)	835 (26.1)	<0.001	178 (20.5)	172 (19.8)	0.715
Antiarrhythmics (Amiodarone, Propafenone, Flecainide, Dronedarone, Sotalol, dofetilide, Disopyramide, Quinidine)	98 (9.7)	150 (4.7)	<0.001	72 (8.3)	68 (7.8)	0.715
Ketoconazole	20 (2.0)	56 (1.8)	0.632	17 (2.0)	20 (2.3)	0.622
Antiplatelets	120 (11.9)	414 (12.9)	0.379	101 (11.6)	110 (12.7)	0.511
Non-steroidal anti-inflammatory drugs	240 (23.8)	706 (22.1)	0.259	201 (23.1)	206 (23.7)	0.775
Number of concomitant medication classes, mean (SD)	3.08 (1.88)	3.20 (1.99)	0.081	3.10 (1.91)	3.09 (1.99)	0.951
Index prescriber specialty, n (%)						
Cardiology	427 (42.3)	693 (21.7)	<0.001	323 (37.2)	310 (35.7)	0.479
Pulmonary medicine	6 (0.6)	26 (0.8)	0.486	6 (0.7)	9 (1.0)	0.439
Hematology	1 (0.1)	0	0.075	1 (0.1)	0	–
Internal medicine	171 (16.9)	868 (27.1)	<0.001	161 (18.5)	153 (17.6)	0.600
Family/general practice	61 (6.0)	344 (10.8)	<0.001	56 (6.4)	65 (7.5)	0.393

(continued)

Table III. (continued).

Characteristic*	Before PSM			After PSM		
	Dabigatran (n=1,010)	Warfarin (n=3,200)	*P* value†	Dabigatran (n=869)	Warfarin (n=869)	*P* value†
Geriatrics	1 (0.1)	1 (0.03)	0.389	1 (0.1)	0	–
Surgery (all types, including vascular surgery)	0	17 (0.5)	0.020	0	2 (0.2)	–
Gastroenterolog	2 (0.2)	6 (0.2)	0.947	1 (0.1)	2 (0.2)	0.564
Neurology	3 (0.3)	11 (0.3)	0.822	3 (0.4)	2 (0.2)	0.655
Emergency medicine	0	16 (0.5)	0.024	0	5 (0.6)	–
Other provider types	338 (33.5)	1,217 (38.0)	0.009	317 (36.5)	321 (36.9)	0.834
Unknown	0	0	–	0	0	–
Multiple	0	1 (0.03)	0.574	0	0	–

COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; MAPD, Medicare Advantage with Part D prescription drug coverage; MI, myocardial infarction; PSM, propensity score match; SD, standard deviation.

*The following pre-index variables were used for PSM: age, gender, plan type, geographic location, index month, Deyo-Charlson comorbidity score, $CHADS_2$ score, $HEMORR_2HAGES$ score, comorbidities (heart failure, diabetes, cardiomyopathy, COPD/emphysema, hyperlipidemia, peptic ulcer/gastroesophageal reflux disease, stroke/transient ischemic attack, hypertension, venous thromboembolism, bleeding), index prescriber specialty, time from first AF claim to index exposure, and concomitant medication use (argatroban, unfractionated heparin, enoxaparin, tinzaparin, dalteparin, fondaparinux, beta blockers, calcium channel blockers, diuretics, other antihypertensives [angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers], antihyperlipidemics, corticosteroids, antidiabetics, antiarrhythmics [amiodarone, propafenone, flecainide, dronedarone, sotalol, dofetilide, disopyramide, quinidine], ketoconazole, antiplatelets, non-steroidal anti-inflammatory drugs).

†2-sample t-test with Satterthwaite adjustment where appropriate (continuous variables) and chi-square test (categorical variables).